Governmental regulatory requirements for “plasma for fractionation” in Europe

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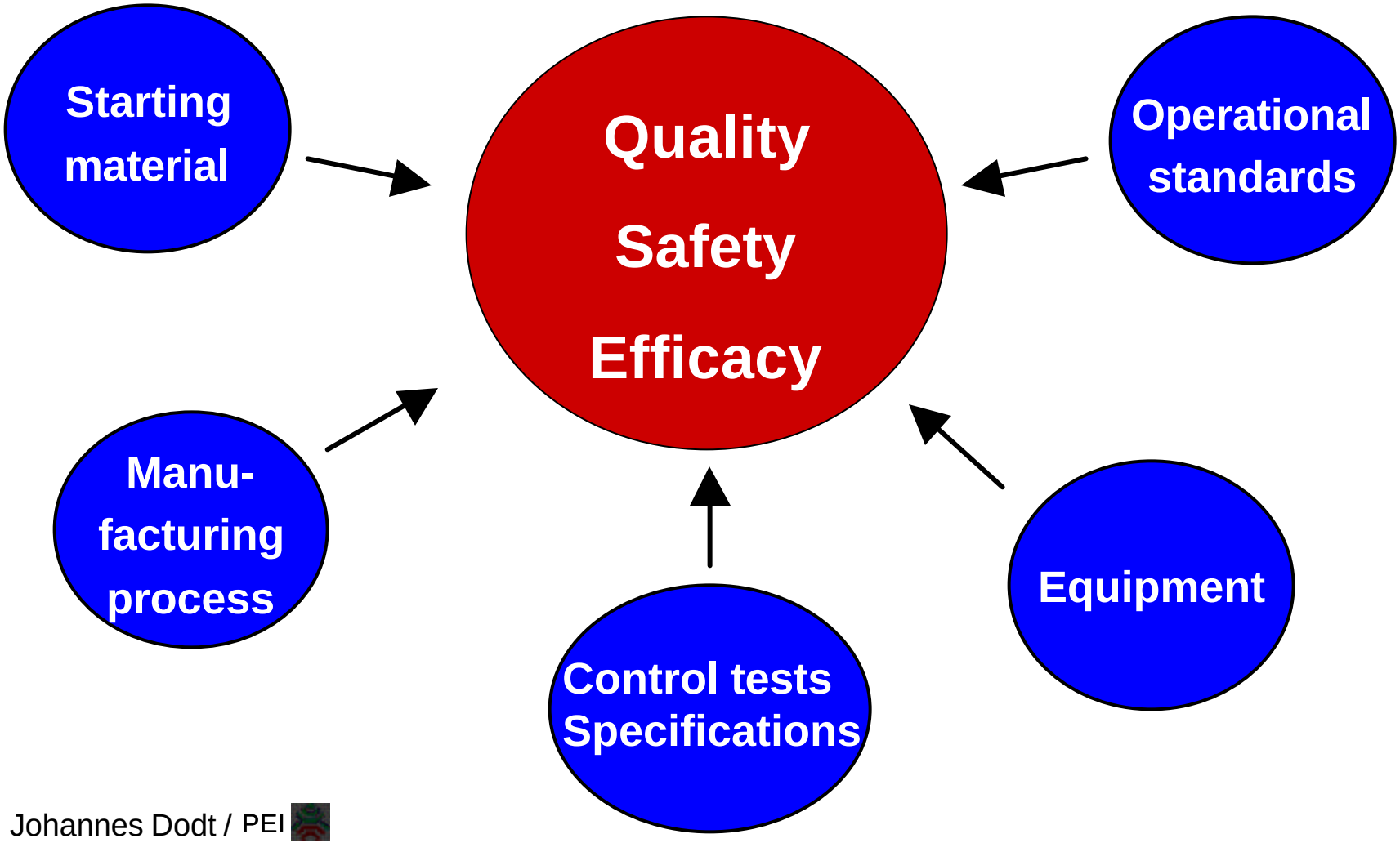
Content

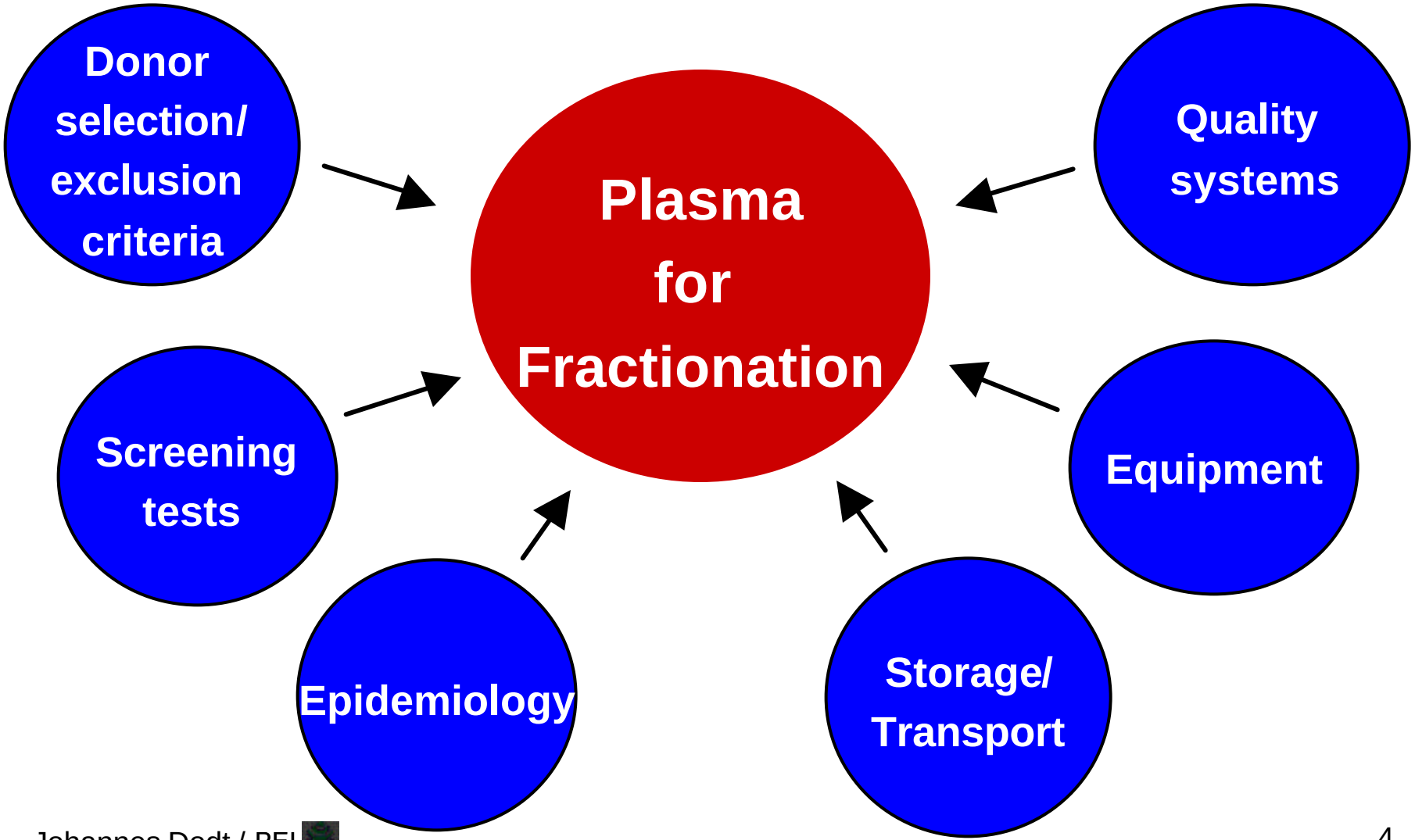
- Importance of plasma for fractionation for the manufacture of blood products
- EU legal background for „Human plasma for fractionation“
- Monograph Ph. Eur. 0853 „Human Plasma for Fractionation“
- Summary

Blood Products

Quality design is an all-embracing concept



Quality of Plasma for Fractionation



EU Legal Background

- **Directive 2001/83/EC**
  on the Community code relating to medicinal products for human use
- **Recommendations No. R (95) of the Council of Europe**
  on the preparation, use and quality assurance of blood components (not legally binding, not for plasma for fractionation)
- **European Pharmacopoeia Monograph 0853**
  Human Plasma for Fractionation
- **CPMP/BWP/269/95 rev. 3**
  Note for guidance on plasma-derived medicinal products

EU Legal Background (February 8, 2005)

- **Directive 2001/83/EC**
  on the Community code relating to medicinal products for human use
- **Directive 2002/98/EC**
  Setting standards of the quality and safety of the collection, testing, processing, storage and distribution of human blood and blood components and ammending directive 2001/83/EC
- **Directive 2004/33/EC**
  Implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements of blood and blood components
- **Recommendations No. R (95) of the Council of Europe**
  on the preparation, use and quality assurance of blood components
- **European Pharmacopoeia Monograph 0853**
  Human Plasma for Fractionation
- **CPMP/BWP/269/95 rev. 3**
  Note for guidance on plasma-derived medicinal products

„Human plasma for fractionation“

- **The scope of Directive 2002/98/EC and its technical annexes (e.g. 2004/33//EC) cover only collection and testing for plasma for fractionation**
- **Standards for „plasma for fractionation“ are covered by the Ph. Eur. monograph 0853**

Directive 2002/98/EC

DIRECTIVE 2002/98/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 27 January 2003

setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC

„In order to ensure that there is an equivalent level of safety and quality of blood components, whatever their intended purpose, technical requirements for the collection and testing of all blood and blood components including starting materials for medicinal products should be established by this Directive.“

Directive 2002/98/EC

- The directive provides a binding common legal frame, which has to be translated into national legislation of member states
- The implementation and application is a duty of member state authorities, the elaboration of technical requirements involves scientific committees in the European Communities
- Transposition: Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive not later than 8 February 2005

Council of Europe Recommendation No. R (95) 15

Guide to the Preparation, Use and Quality Assurance of Blood Components.

Purpose	**Transfusion**	
Collection method	**Whole Blood**	**Apheresis**
Time from collection to freezing	**6 hrs but nmt =18 hrs** **If 20-24°C up to 24hrs**	**within 6hrs** **If 20-24°C up to 24hrs**
Freezing temperature	**To < -30 °C within 1 hr**	**To < -30 °C within 1hr**
Storage, expiration	**-18 °C to -25 °C: 3 months** **<-25 °C: 24 months**	
Shipping temperature	**see above "storage"**	
Allowable deviation	**None**	

European Pharmacopoeia Monographs

- **European Pharmacopoeia has the task of laying down common standards for the composition and preparation of substances (e.g. excipients, starting materials) used in the manufacture of medicines**
- **Medicinal products, marketed in the EU (Member states of the European Pharmacopoeia) have to comply with relevant European Pharmacopoeia (Ph. Eur., EP) monographs and methods**
- **The Pharmacopoeia "monographs" have force of law in the EU, replacing the old national pharmacopoeias**
- **The EP monographs and assay methods for blood products are elaborated by the expert group 6B**

http://www.pheur.org/

Group 6B and Ph. Eur. Monograph 0853

Since September 1991:

- **25 Meetings**
- **Plasma for fractionation: 18 x on agenda**

The Issue

?

Scope of FDA Workshop and Ph. Eur. 0853

Scope of Workshop:

- **Freezing and storage temperature**
- **Time to freezing (dependent on final product?)**
- **What should the recovered plasma component be called?**
- **Expiration dating for recovered plasma?**
- **Distinguish recovered plasma from source plasma?**

- **How does the European Pharmacopoeia deal with these issues?**

Definition - Human Plasma for Fractionation

Definition:

Plasma for fractionation is the liquid part of human blood after separation of the cellular elements from blood collected in a receptacle containing an anticoagulant, or separated by continuous filtration or centrifugation of anticoagulated blood in an apheresis procedure; it is intended for the manufacture of plasma-derived medicinal products.

- **One standard: Plasma for fractionation**
- **Plasma for fractionation can be obtained either from whole blood donations or from plasmapheresis.**

Monograph “Human Plasma for Fractionation”

Monograph

Develop standards for plasma for fractionation which

- **Provide assurance about the high quality (protein integrity) of the source material for the manufacture of blood products**
  and
- **Consider the need of industry**

Time to Freezing

Edition (year)	Condition	Change/Rationale
4.5 (2003)	4.5 is the current edition. Same condition as in edition 3 (Suppl. 2001).	
3 (Suppl. 2001)	Depends on the characteristics of the protein in plasma and collection method: 1. labile in plasma: as soon as possible but at the latest within 24 hrs (plasma obtained by plasmapheresis and from whole blood) 2. non-labile in plasma: as soon as possible but at the latest within 72 hours (plasma obtained from whole blood)	1. Clarification: Components which are labile in plasma are concerned 2. It was recognised that plasma obtained from whole blood after its expiry was not used any longer for fractionation. Based on manufacturing practice it was decided to define a standard for proteins that are non-labile in plasma
3 (1997)	Depends on the final product and collection method: labile products: as soon as possible but at the latest within 24 hrs (plasma obtained by plasmapheresis and from whole blood) non-labile products: Separation within 5 days of the expiry date of whole blood (plasma obtained from whole blood)	

Scientific Evidence for Time to Freezing

- **Most papers focus on labile components, e.g. coagulation factor VIII, factor V**
- **It has been show that time to freezing is crucial for recovery of labile components**
- **Preservation of labile components in plasma**
  - **optimal up to 6 hrs after donation**
  - **loss of factor VIII activity about 15% during 16-24 hrs storage before freezing**
  - **additional loss when stored longer than 24 hrs**

Selected literature:

1. Illert, W.E. (1986): Stabilität von gerinnungsaktivem Frischplasma (stability of fresh frozen plasma), Krankenhauspharmazie 12, 530-535
2. Wensley, R.T. and Snape, T.J.´(1980): Preparation of improved cryoprecipitated Factor VIII concentrate, Vox Sang. 38, 222-228
3. Smith, J.K., Snape, T.J., Haddon, M.E., Gunson, H.H. and Edwards, R. (1977): Methods for assessing factor VIII content of stored fresh frozen plasma intended for the preparation of factor VIII concentrates

Freezing Temperature

Edition (year)	Condition	Change/Rationale
4.5 (2003) current	4.5 is the current edition. Same condition as in edition 3 (Suppl. 2001)	
3 (Suppl. 2001)	1. When obtained by plasmapheresis or from whole blood … plasma intended for the recovery of proteins that are labile in plasma is frozen by cooling rapidly at -30°C or below …" 2. "When obtained from whole blood plasma intended solely for the recovery of proteins that are non-labile in plasma is separated from cellular elements and frozen at -20°C or below."	1. Clarification: Components which are labile in plasma are concerned. 2. Addition of standard regarding manufacture of components which are non-labile in plasma
3 (Suppl. 1998)	"Plasma intended for the manufacture of coagulation factors and other labile derivatives …. is frozen by cooling rapidly **at** -30°C or below."	
3 (1997)	"Any plasma intended for the manufacture of coagulation factors or other labile components is processed shortly after separation or collection or it is frozen by cooling rapidly **to** a temperature of -30°C or below."	The temperature was set in accordance with that for plasma for transfusion. Core temperature -30°C.

Scientific Evidence for Freezing Temperature

- **Optimal preservation of proteins in plasma: flash freezing**
  - **plasma for transfusion: ?to -30°C (core temperature) within 60 min**
  - **plasma for fractionation: ? time for freezing process is not defined, ? at -30°C (frozen below the eutectic point)**
- **No data in favour of freezing at -20°C**
  - **group 6B fixed temperature similar to that for plasma for transfusion,**
  - **revision considered the need of industry**
  - **industry was asked to propose a higher temperature on the basis of scientific data. No data available, but Industry is satisfied with monograph**

Selected literature:

- Rock, G.A. and Tittley, P. (1977): The effect of temperature variations on cryo-precipitate, Transfusion 19, 86-89
- Carlebjörk, G. , Blombäck, M. and Philstedt, P. (1986): Freezing of plasma and recovery of factor VIII , Transfusion 26, 159-162
- Farrugia, A. and Prowse, C. (1985): Studies on the procurement of blood coagulation factor VIII: effects of plasma freezing rate and storage conditions on cryoprecipitate quality, J Clin Pathol 38, 433-437
- Wensley, R.T. and Snape, T.J.´(1980): Preparation of improved cryoprecipitated Factor VIII concentrate, Vox Sang. 38, 222-228
- Akerblom, O., Bremme, K., Dackland , A.-L., Fatah, K., Suontaka, A.-M., Blombäck, M. (1992): Freezing technique and quality of fresh frozen plasma, Infusionstherapie 19, 283-287

Storage Temperature

Edition (year)	Condition	Change/Rationale
4.5 (2003) Current edition	Store at or below –20°C	No change
3 (Suppl. 1998)	Store at or below –20°C	It was recognised and agreed that storage of plasma for fractionation at or below –20°C is possible to prepare products of suitable quality.
3 (1997)	Store at or below –25°C	▪ Eutectic point at –23°C ▪ Controversial discussion whether repeated passage across the eutectic point might lead to degradation of proteins ▪ Contrary to US regulations and WHO documents

Scientific Evidence for Storage Temperature

- **Stability studies showed stability of proteins that are labile in plasma when the plasma was stored at -20°C**

Selected literature:

- Kotischke, R., Morfeld, F., Kirchmaier, C.-M., Koerner, K. and Köhler, M. (2000): Stability of fresh frozen plasma: Results of 36-month storage at -20°C, -25°C, -30°C and -40°C, Infus Ther Transfus Med 27, 174-180
- Illert, W.E. (1986): Stabilität von gerinnungsaktivem Frischplasma (stability of fresh frozen plasma), Krankenhauspharmazie 12, 530-535
- Koerner, K. and Stampe, D. (1984): Die Stabilität von Faktoren des Gerinnungssystems im tiefgefrorenen Frischplasma während der Lagerung bei -20°C und -40°C (Stability of coagulation factors during storage of fresh frozen plasma at -20°C and -40°C), Infusionstherapie 11, 46-50

Storage and Transport Conditions

Edition (year)	Condition	Change/Rationale
4.5 (2003) Current edition	Store and transport frozen plasma at or below –20°C; the plasma may still be used if the temperature is between –20°C and –15°C for not more than a total of 72 h without exceeding –15°C on more than one occasion as long as the temperature is at all times –5°C or lower.	Clarification Adapted to the need of manufacturers.
3 (Suppl. 1998)	Store frozen at or below –20°C; the plasma may still be used for fractionation if a temperature of –20°C is exceeded on at most one occasion for not more than 72 hours and if the plasma is at al times maintained at a temperature of –5°C or lower	Does not mention time for transport any longer.
3 (1997)	Store frozen plasma at –25°C. During shipping which must not last longer than 4 weeks, maintain the plasma at or below –20°C; this temperature is maintained as far as possible during shipping but the plasma may still be used for fractionation if the temperature is exceeded on at most one occasion for not more than 72 hours and if the plasma is at all times maintained at a temperature of –5°C or lower.	

Scientific Evidence for Storage and Transport Conditions

- **Excursions are allowed which guarantee that the plasma is still frozen and suitable for fractionation**

Selected literature:

- Farrugia, A. and Prowse, C. (1985): Studies on the procurement of blood coagulation factor VIII: effects of plasma freezing rate and storage conditions on cryoprecipitate quality, J Clin Pathol 38, 433-437
- Akerblom, O., Bremme, K., Dackland, A.-L., Fatah, K., Suontaka, A.-M., Blombäck, M. (1992): Freezing technique and quality of fresh frozen plasma, Infusionstherapie 19, 283-287

Expiration

- **Monograph 0853 does not mention an expiration period for plasma for fractionation**
- **Is this a matter of concern?**
- **<u>In practice not</u>**
  - **According to Marketing Authorisation: 2-3 years**
  - **Data from batch release**
  - **Regulatory authorities: Safety, e.g. state-of-the-art screening**
  - **Marketing Authorisation Holder: Safety, economical reasons**

Plasma for Fractionation - Monograph Text

“When obtained by plasmapheresis, plasma intended for the recovery of proteins that are labile in plasma is frozen by cooling rapidly at - 30 °C or below as soon as possible and at the latest within 24 h of collection.

When obtained from whole blood, plasma intended for the recovery of proteins that are labile in plasma is separated from cellular elements and is frozen by cooling rapidly at - 30 °C or below as soon as possible and at the latest within 24 h of collection.

When obtained from whole blood, plasma intended solely for the recovery of proteins that are not labile in plasma is separated from cellular elements and frozen at - 20 °C or below as soon as possible and at the latest within 72 h of collection.”

Plasma for Fractionation – Summary Table

	Plasma for Fractionation	
Purpose	Manufacture of proteins which are labile in plasma	Manufacture of proteins which are not labile in plasma
Collection method	Plasmapheresis or whole blood	Whole blood (Plasmapheresis?)
Time to freezing	≤24 hrs	≤72 hrs
Freezing Temp.	at ≤-30 °C	at ≤-20 °C
Storage Temp.	≤-20 °C	
Shipping Temp.	≤-20 °C	
Allowable deviation	-20 °C to -15°C at one or more occasions; one time > -15 °C but never > -5 °C Total time exceeding -20°C: 72 hrs	

Open Issues not Discussed

- **Definition of factors which are considered labile or not labile is not given:**
  - **Common sense, e.g. coagulation factors are labile, albumin and immunoglobulins are non-labile?**

Harmonisation

Letter of group 6B regarding the "*Revisions to Labeling and Storage Requirements for Blood and Blood Components, Including Source Plasma*"(Federal Register / Vol. 68, No. 146 on July 30, 2003)

"The European Pharmacopoeia (Ph. Eur.), a part of the European Department for the Quality of Medicines (EDQM) located in Strasbourg (France), is the competent regulatory authority laying down requirements for plasma for fractionation, which are mandatory in all member states of the Council of Europe, which include all member states of the European Communities and further countries within and beyond the European continent. In order to enable the exchange of plasma for fractionation, intermediates and medicinal products produced thereof, it appears desirable to avoid discrepant regulatory requirements, which might hinder that exchange. To this end, the proposals laid down in the above mentioned document would have an impact on the possibility of importation of source plasma and derivatives into the area covered by the Council of Europe. Therefore, the Ph.Eur. takes the opportunity to respectfully submit the following comments worked out by its expert group 6B (chair: Prof. Rainer Seitz, Paul-Ehrlich-Institut), and to suggest that the FDA may considers the requirements laid down in the relevant PhEur monograph on Human Plasma for Fractionation."

Harmonisation

- **EU Authorities are interested in harmonisation of requirements for plasma for fractionation**
  - Same quality in EU and USA
- **Industry would appreciate harmonisation**
  - Global operating
  - Easier logistics
  - Maximum flexibility and availability
- **Industry is satisfied with regulations in EU, which are evidence based and well balanced**
- **How do we maintain harmonised regulations?**

Conclusions

- **For “plasma for fractionation” there is one standard in the EU**
  - Collection and testing is regulated by Directive 2002/98/EC
  - Production is regulated by Ph. Eur. Monograph 0853
- **EU would highly appreciate harmonisation of a standard for plasma for fractionation**
  - Advantage for regulators and industry